REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 2, 5-13, 18-26, 56 and 57 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 2, 5-13, 18-26, and 56-57 have been rejected under 35 U.S.C. §112, first paragraph, because the examiner holds that the specification, while being enabling for a method of preparing $CD34^+$ cells *in vivo*, said method comprising administering to a donor a composition comprising growth hormone and a composition comprising G-CSF, and isolating $CD34^+$ cells from the donor, is not enabling for a method of preparing $CD34^+$ cells *in vivo* by administering to a donor a composition comprising growth hormone derivatives or any factor inducing growth hormone release and a composition comprising G-CSF and isolating the population of circulating cells. The examiner further refers to two different growth hormone derivatives having opposite effects. It is the examiner's position that the issue is not the existence of growth hormone releasing factors but the fact the applicants have not shown a single growth hormone releasing factor which increases the circulating $CD34^+$ cells when administered in conjunction with G-CSF. The examiner concludes that there is insufficient enablement for "all" possible growth

hormone derivatives and factors that induce growth hormone release. This rejection is respectfully traversed.

Claim 2 is now amended to positively recite that the growth hormone derivative has the activity of growth hormone. Accordingly, the recited growth hormone derivative would not encompass a growth hormone derivative which acts as an antagonist and inhibits normal growth hormone activity. By this recitation in claim 2, it is quite clear to those of skill in the art which growth hormone derivatives, from amongst the numerous growth hormone derivatives having growth hormone activity, would be encompassed by the present claims. Accordingly, growth hormone derivatives having growth hormone activity are indeed enabled by the guidance provided in the instant application in conjunction with the wealth of knowledge in the art regarding growth hormone derivatives.

Regarding the recitation of a factor which induces growth hormone release, the fact that applicant does not have working examples with such a factor should not be reason for lack of enablement as applicant is allowed to be prophetic for the subject matter claimed. Factors that induce the release of growth hormone were well known at the time the invention was made, as evidenced by Appendix A listing prior art references disclosing such factors and the attached front pages of U.S. patents relating to growth hormone releasing hormone and

functional derivatives thereof. Accordingly, all that is required to satisfy the enablement requirement is one of skill in the art finding it quite credible that any factor inducing growth hormone release would reasonably be expected to have the same effect as growth hormone itself on enhancing the mobilization or peripheralization effect of G-CSF. Clearly, it would be reasonable to expect that administering a factor that induces growth hormone release would have similar effect to administering growth hormone *per se* since growth hormone would be released in the subject as a result of the administration of the inducing factor.

What applicant has discovered is the unexpectedly superior result that growth hormone enhances the effect of G-CSF. It would be unfair for applicant to be left unprotected against a third party who uses any of a number of factors inducing growth hormone release to practice the present invention, as such factors are well known in the art, after specifically teaching such use in the instant application.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 2, 5-13, 18-26, and 56-57 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Haas et al. (1995) in view of Murphy et al. (1992). The examiner states that applicants have only addressed the Murphy et al. reference but

not the Haas reference which teaches that the administration of G-CSF increased the level of circulating $CD34^+$ cells. The examiner takes the position that the combined teachings of Haas et al. and Murphy et al. render the claimed invention obvious because Haas et al. teach that the administration of G-CSF increased the level of circulating $CD34^+$ cells, and Murphy et al. teach that growth hormone exerts a significant effect on hematopoietic progenitor cells. The examiner concludes that one of ordinary skill in the art would have an expectation of success that the administration of these agents together would have synergistic effect. This rejection is respectfully traversed.

Applicant does not argue against the disclosure of Haas as applied by the examiner because this is in fact the state of the art that the present invention seeks to improve with applicant's discovery of surprisingly superior results. Rather, applicant disagrees with the examiner's interpretation of Murphy's disclosure and its application to suggest that the administration of the G-CSF of Haas and the growth hormone of Murphy together would be expected to have synergistic effect. Murphy teaches only the peripheral engraftment of T cells, which are <u>differentiated</u> or at least partly differentiated in the case of pre-T cells, not hematopoietic progenitor and stem cells. One of skill in the art would certainly not confuse Murphy's teaching regarding T cells as a suggestion that growth hormone would

function synergistically with G-CSF for undifferentiated $CD34^+$ hemapoietic progenitor and stem cells (see Haas, page 251, middle of left column, where it is disclosed that the $CD34^+$ antigen is expressed on all human hematopoietic progenitor and stem cells). Accordingly, one of ordinary skill in the art would not extrapolate the disclosures of Murphy regarding the action of growth hormone on T-cells with Haas' disclosure of the mobilizing effect of G-CSF on hemapoietic progenitor and stem cells to arrive at the surprising finding that growth hormone enhances the mobilization and peripheralization effect of G-CSF on undifferentiated $CD34^+$ hemapoietic progenitor and stem cells.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 2, 5-13, 18-26 and 56-57 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

The examiner considers the claim language "… to further increase in said donor the number of circulating $CD34^+$ cells… beyond that achieved by G-CSF alone …" to render claim 2 indefinite because the claim does not recite what is the number of circulating $CD34^+$ cells obtained after G-CSF administration and how much more the administration of the growth hormone should achieve.

All that is required in the claim is an improvement, i.e., synergistic enhancement, of the effect of G-CSF by growth hormone, a derivative thereof, or a factor inducing release of growth hormone, as would be well recognized and understood by those of skill in the art. Clearly, such an improvement (increase in number of circulating $CD34^+$) would not be considered to be negligible (if that is what concerns the examiner) by those of skill in the art given the disclosure in Example 7, page 56 of the specification that, following chemotherapy there is a surprising doubling or tripling in the mobilization of circulating $CD34^+$ cells in the bloodstream when growth hormone is administrated with G-CSF (cycle 2) versus the control (cycle 1) where G-CSF is administered alone.

Regarding claims 7, 10 and 12, where the examiner finds the use of "about" to be indefinite for the metes and bounds of the amount of cells, it is clear that the use of the phrase "or more" means that it can be any amount more than the specifically recited number. This then leads to how far below the specifically recited number the term "about" would encompass. The Court of Appeals' decision in *Georgia Kaolin Co. v. Thiele Kaolin Co.* 108 USPQ 61, which is cited in numerous later decisions, holds that:

> In this connection, we note that the use of such similar, indefinite terms and phrases and "about", "sufficient *** to enhance", slight excess, substantial space, etc., to

> permit a reasonable tolerance in commercial practice of inventions, has been held insufficient to invalidate claims for alleged ambiguity in their disclosure, so that we do not feel justified, upon this practically de novo judicial review on validity, in holding the claims invalid upon this ground. There are decisions recognizing that a patentee is not inexorably required, upon penalty of forfeiting his statutory monopoly, either precisely to describe, or fully appreciate, the nature of the changes wrought by his process which result in production of the product desired. (emphasis added)

Accordingly, some reasonable tolerance in practicing the claimed invention by the use of the term "about" is permitted.

Regarding claim 56, the recitation of "... is administered at a different time than..." is not indefinite as those of skill in the art would fully understand what is meant by "a different time" in view of the disclosure as a whole and particularly in view of the disclosure on page 13, lines 16-19, which teaches that the administration of growth hormone is done three times a day and the administration of G-CSF is done daily (once a day). Accordingly, those of skill in the art would immediately recognize the metes and bounds of what is intended by the claim language in claim 56. If the examiner instead prefers the language of "separate" administration of growth hormone and G-CSF without regard to the timing, applicant would consider amending claim 56. However, at present, applicant firmly believes that the metes and bounds of claim 56 are clear to those of skill in the art.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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